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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,179	04/06/2004	Andrew Pakula	ANP-00114.P.5.1	7367
24232 7590 06/11/2007 DAVID R PRESTON & ASSOCIATES APC 5850 OBERLIN DRIVE SUITE 300 SAN DIEGO, CA 92121			EXAMINER LUNDGREN, JEFFREY S	
			ART UNIT 1639	PAPER NUMBER
			MAIL DATE 06/11/2007	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/820,179	PAKULA ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Jeff Lundgren	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 05 March 2007.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 66-107 is/are pending in the application.
- 4a) Of the above claim(s) 67-94, 96-101 and 103-107 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 66, 82, 95 and 102 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |                                                                                        |                                                                   |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>5/21/04 and 7/2/04</u> .                                      | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of the Claims***

Claims 66-107 are pending in the instant application; claims 67-94, 96-101 and 103-107 are withdrawn as being directed to a non-elected species; claims 66, 95 and 102 read on the elected species, and are the subject of the Office Action below.

### ***Information Disclosure Statement***

The information disclosure statement filed February 3, 2003, fails to fully comply with 37 CFR 1.98(a)(2), which requires: (i) a legible copy of each cited foreign patent document; and (ii) a copy of an English-language translation of all non-English-language documents, or portion thereof. Accordingly, certain documents cited on the Form-1449 provided without a copy, or provided in a language other than English, have been lined through and have not been considered.

Documents cited on the Form-1449 which have been considered by the Examiner are indicated by the signing of the Examiner's initials in the appropriate box on the return Form-1449.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 66, 82, 95 and 102, are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 66 is indefinite for reciting the phrase "plurality of ligands *not known* to bind" because it is not clear how one of ordinary skill in the art would determine which ligands are already "known" to bind from those that are "not known" to bind (see step a). Correction is required.

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Claim 66, step *f*, is indefinite because it is not clear what step Applicants' are actually performing. For example, if by the end of step *f* an identification is performed, such language should be used.

Claim 102 is indefinite for reciting the phrase "possible development" because the metes and bounds of this limitation cannot be determined. It is not clear if this limitation reads on someone's intentions or if there is a physical act that is involved. Correction is required.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 66, 82, 95 and 102, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Volkin *et al.*, Harnessing Biotechnology for the 21<sup>st</sup> Century:298-302 (1992), in view of Agrafiotis *et al.*, U.S. Patent No. 5,463,564, issued on October 31, 1995.

Claim 66 is directed to a method for screening ligands, for possible development as new pharmaceuticals which comprises: (a) selecting a plurality of compounds not known to bind to said target protein; (b) separately incubating each of said selected compounds and said target protein to produce a plurality of test combinations; (c) incubating said target protein in the absence of said selected compounds to produce a control combination; (d) subjecting each of said test combinations and said control combination to conditions to cause detectable fractions of

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said target protein to unfold to a measurable extent; (e) determining the fractions of said target protein in each combination that exists in an unfold state, a folded state, or both; (f) comparing the determination made in step (e) between said test combination and said control combination for said selected compounds, wherein if said target protein is present in the folded state to a greater extent in said test combination than in said control combination, said selected compound binds to the target protein; (g) repeating steps (a) through (f) with more than 1,000 of said selected compounds; and (h) selecting as a lead compound any selected compound from each test combination in which said target protein is present in the folded state to a greater extent in said test combination than in said control combination.

Volkin teaches a method for assaying the binding of a plurality of ligands to proteins (see page 298), namely, acidic fibroblast growth factor (aFGF) binding to heparin and other heparin-like compounds to study the effects of these compounds on the structural stability of aFGF. Volkin teaches the titration of aFGF with heparin and measures the degree of unfolding (see Fig. 1), and carries out the same assay with other heparin-like compounds (see Table 2).

As in claim 82, Volkin teaches measuring the extent of unfolding as a result based on heating (see Table 1). As in claim 95, sumarin is used a fluorescent probe added to the test combination (see Figure 1, and description thereof). As in claim 102, the compounds studied by Volkin are useful as potential therapeutics.

Although Volkin teaches multiple compounds that influence protein folding/unfolding as studied by fluorescence spectroscopy, Volkin does not explicitly teach the claimed "more than one thousand" ligands as in claim 66.

Agrafiotis teaches a system and method of automatically creating, identifying and selecting compounds for a chemical library based on observed physicochemical properties:

"The present invention relates generally to the generation of chemical entities with defined physical, chemical or bioactive properties, and particularly to the automatic generation of drug leads via computer-based, iterative robotic synthesis and analysis of directed diversity chemical libraries."

Agrafiotis, col. 1, lines 9-13. Agrafiotis also teaches that the initial libraries for compound screening in the art of combinatorial chemistry have compound members of the number 1000 to 5000 (col. 19, lines 10-16).

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One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Volkin and Agraftotis are directed to the art of combinatorial chemistry. One of ordinary skill in the art would have been motivated to utilize the large library approach of Agraftotis with the method of Volkin for increasing the likelihood of finding successful candidates to aFGF. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

### ***Double Patenting***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 66, 82, 95 and 102 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-47 of U.S. Patent No. 5,679,582, in view of Volkin *et al.*, Harnessing Biotechnology for the 21<sup>st</sup> Century:298-302 (1992), in view of Agrafiotis *et al.*, U.S. Patent No. 5,463,564, issued on October 31, 1995.

Volkin teaches a method for assaying the binding of a plurality of ligands to proteins (see page 298), namely, acidic fibroblast growth factor (aFGF) binding to heparin and other heparin-like compounds to study the effects of these compounds on the structural stability of aFGF. Volkin teaches the titration of aFGF with heparin and measures the degree of unfolding (see Fig. 1), and carries out the same assay with other heparin-like compounds (see Table 2).

As in claim 82, Volkin teaches measuring the extent of unfolding as a result based on heating (see Table 1). As in claim 95, sumarin is used a fluorescent probe added to the test combination (see Figure 1, and description thereof). As in claim 102, the compounds studied by Volkin are useful as potential therapeutics.

Although the '582 patent and Volkin teach multiple compounds that influence protein folding/unfolding as studied by fluorescence spectroscopy, neither the '582 patent nor Volkin explicitly teach the claimed "more than one thousand" ligands as in claim 66.

Agrafiotis teaches a system and method of automatically creating, identifying and selecting compounds for a chemical library based on observed physicochemical properties:

"The present invention relates generally to the generation of chemical entities with defined physical, chemical or bioactive properties, and particularly to the automatic generation of drug leads via computer-based, iterative robotic synthesis and analysis of directed diversity chemical libraries."

Agrafiotis, col. 1, lines 9-13. Agrafiotis also teaches that the initial libraries for compound screening in the art of combinatorial chemistry have compound members of the number 1000 to 5000 (col. 19, lines 10-16).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of the '582 patent claims, Volkin and

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Agrafiotis are directed to the art of combinatorial chemistry. One of ordinary skill in the art would have been motivated to utilize the large library approach of Agrafiotis with the method of Volkin for increasing the likelihood of finding successful candidates to aFGF. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

### *Conclusions*

No claim is allowable.

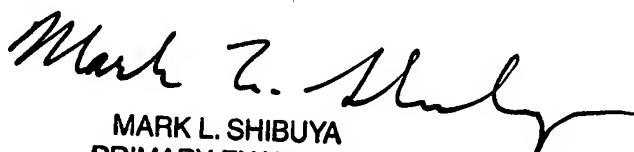
If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipso verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL

  
MARK L. SHIBUYA  
PRIMARY EXAMINER